IND 3

145 - 220 - 1807

#22

3/22/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

January 22, 1996

In re Application of:	Byoung Se Kwon
Serial No.:	08/012,269
Filed:	2/01/93
For:	NEW RECEPTOR, MONOCLONAL ANTIBODY, LIGAND PROTEIN AND METHODS FOR USE
Examiner:	M. Mosher
Art Unit:	1807
Docket No.:	IND3

APPEAL BRIEF

Honorable Commissioner Of Patents And Trademarks
Washington, DC 20231

This application is before the Honorable Board of Appeals on appeal from the final rejection by the Examiner dated August 21, 1995, wherein claims 1-3 and 22 were finally rejected.

This brief is filed in triplicate and the fee of $145.00 for filing is attached. A request for an oral hearing is attached hereto along with the appropriate fee.

(1) STATUS OF CLAIMS

Claims 1-3 and 6-22 are pending in the application. Claims 6-21 have been withdrawn from consideration pending the filing of a divisional or continuation application and claim 4

and 5 were cancelled by the applicant. Claim 22 has been rejected under 35 U.S.C. §112, second paragraph. Claims 1-3 and 22 have been rejected under 35 U.S.C §101. Claims 1-3 and 22 have been rejected under 35 U.S.C §112, first paragraph. Claims 1-3 and 22 have been rejected under 35 U.S.C §103.

(2) STATUS OF AMENDMENTS

The amendments made in the response dated December 17, 1993 were entered. The amendment to the specification made in the response dated July 1, 1994 after the final rejection dated July 1, 1994 were entered. The amendments to the claims made in the response dated April 10, 1995 were entered.

(3) SUMMARY OF THE INVENTION

The present invention is a novel cDNA sequence, 4-1BB, that encodes a receptor protein. The applicant used a differential screening process to isolate 16 subset clones. Fourteen of the initial isolates were sequenced and found to be five distinct species. Of these five, three were discovered to be known proteins and the remaining two were novel sequences. 4-1BB was one of the novel sequences.

The protein encoded by 4-1BB was discovered to be a receptor. Cells expressing 4-1BB stimulate B-cell proliferation, therefore, recombinant 4-1BB is useful as an agent to suppress the immune response during organ transplantation by binding on the receptors to 4-1BB. A monoclonal antibody 53A2 against 4-1BB can be used to enhance cross-linking of T-cells and T-cell proliferation.

References Relied Upon or Made of Record by the Examiner

a) Kwon *et al.*, Proc. Natl. Acad. Sci. 86:1963 (1989).

(4) ISSUES

I. The first issue is whether claim 22 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention under 35 U.S.C. §112, second paragraph

II. The second issue is whether the utility recited in the specification is sufficient to satisfy the requirements of 35 U.S.C. §101.

III. The third issue is whether the specification provides an adequate written description and an enabling disclosure for claim 1-3 and 22 under 35 U.S.C. §112, first paragraph.

IV. The third issue is whether claims 1-3 and 22 are anticipated by Kwon *et al.* (1989) under 35 U.S.C. §102.

(5) GROUPING OF CLAIMS

The rejected claims do not stand or fall together.

Claims 1-3 are argued as a group and stand or fall together.

Claim 22 is argued separately.

(6) ARGUMENT

With Respect to Issue I

I. The rejected claim 22 as indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention under 35 U.S.C. §112, second paragraph. This rejection is respectfully traversed.

Claim 22 recites a DNA that encodes an amino acid shown in Figures 2a and 2b and probes that could be used to isolate such a sequence. Thus the claimed DNA is readily identifiable by all those skilled in the art and examples of a sequence and probes are taught in Figures 2a and 2b and on page 17, lines 26-31.

The intercrine ß superfamily is referred to in the application and the conserved sequence fragments are identified in the application on Page 38, line 28 - Page 39, line 16, (see figure 17) and would make the most likely candidates for probes. This is well known and inherent from the information provided to anyone skilled in the art. Those skilled in the art know how to select probes from a known sequence. The modifications that can be made to the cDNA sequence without affecting the encoded amino acid are easily determined merely by looking on a table listing the codons for each amino acid in any biochemistry book.

For reasons set forth above, the rejection of claim 22 under 35 U.S.C. § 112, second paragraph, is believed to be in error. Therefore, the reversal of the Examiner's rejection is requested.

With Respect to Issue II

The Examiner rejected claims 1-3 and 22 under 35 U.S.C. §101 arguing that the specification did not recite a patentable utility. This rejection is respectfully traversed.

Referring to the rejection, the Examiner states that:

> "Applicant argues that 4-1BB is known to have biological activity in the immune system, and therefore it inherently has utility. However, the instant specification does not teach a utility in definite and currently available form. Applicant's arguments regarding use in research amount to an argument that the compound can be used in research in order to

determine the effect on the immune system of 4-1BB or compounds that interfere with 4-1BB."

The specification provides detailed analysis of the expression and function of the 4-1BB gene and protein. 4-1BB is an inducible receptor-like protein expressed in both cytolytic and helper t-cells, PMA-treated spleen cells, heart cells, kidney cells and the brain. (see Page 25, lines 10-13; Page 39, line 17 - Page 43, line 9)

The steroid compound that was made by the applicant's claimed process in *Brenner v. Manson* did not have any biological activity. It was not a steroid compound know to be produced or utilized in any biological organism. This is not true of the claimed cDNA to 4-1BB. 4-1BB is expressed in murine cells as part of the immune system. There is an inherent utility for a cDNA encoding a protein that is involved in the murine immune system. 4-1BB is known to have biological activity in the immune system. The parent application filed 07/267,577 teaches that 4-1BB is a novel protein expressed differentially in T-cells.

The Examiner is overly concerned about the function of 4-1BB *in-vivo*. The Examiner appears to be more concerned with how a mouse uses 4-1BB naturally, rather than how the claimed cDNA can be used by those skilled in the art. Such emphasis is inappropriate. The proper question is whether the applicant's have taught how one of ordinary skill in the art can put the invention to use.

Specifically, the applicant's teach that the claimed cDNA can be incorporated into an expression plasmid and the protein 4-1BB or a fusion protein can be expressed. The fusion protein is useful for finding ligand proteins for 4-1BB. The fusion protein is a tool that is useful in further characterizing the immune system. These tools are useful in the same way that a microscope is useful in learning more about a bacterium. The fact that a product can be used in research does not mean that it has no utility.

Researchers can test various compounds to see if the compounds affect 4-1BB expression or activity. If a compound showed such an effect it would be a concern with regard to use in humans unless such an affect on activity or expression was desired. Thus the claimed

cDNA is a tool that allows researchers to directly test whether compounds affect the expression or activity or 4-1BB. Those compounds not intended to have an affect on the immune response, but that still affected 4-1BB expression or activity could be flagged as problematic. Those skilled in the art would know that the claimed cDNA could be used for such assays and would know how to create such an assay.

The Applicant's have alleged that the cDNA can be used to create a recombinant protein which can be used to create a mAb to 4-1BB. This mAb has been shown to include cross-linking in T-cells and therefore enhance T-cell activation and proliferation. This product has usefulness in culturing of T-cells as well as therapeutic uses. Cross-linking is necessary for the successful culturing of T-cells. The Examiner responds to this by stating that:

> "there is no evidence an record that a monoclonal antibody having these characteristics can be made reproducibly using expression products of the instant cDNA, nor teachings that the activation **is** useful for more than a specific class of T cells, nor teachings of how to use the activated T cells."

It is unclear whether the Examiner does not believe that the applicant actually used the recombinant 4-1BB to raise the mAb (53A2) deposited with ATCC, or that the applicant actually observed T-cell activation and proliferation when conducting the experiments. The disclosure describes these experiments in great detail, specifically, pages 49 and 50 discuss the results of raising antibodies against 4-1BB.

The Examiner's statements are not supported by any objective evidence contradicting the teachings of the specification. *In re Langer*, 503 F.2d 1380, 1391 (CCPA 1974) states:

> "a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirements of §101 for the entire claimed subject matter unless there is

reason to question the objective truth of the statement of utility or its scope."

The Examiner has not stated any reason to question the objective truth of the applicant's allegations of utility. Once an assertion of utility is made the Examiner can only rebut the assertion with objective evidence. The Examiner conclusory statements are insufficient.

Crosslinking of 4-1BB on anti-CD3-stimulated T cells with the monoclonal antibody, 53A2, resulted in a dramatic enhancement of T cell proliferation. (Page 43, lines 12-26) This is not speculative, this activity was demonstrated conclusively by the disclosed data. What is speculative is whether 4-1BB's **primary** purpose in mice is to regulate T cell proliferation, but this does not change the fact that 4-1BB effects on T cell proliferation. This may just be an extremely useful side effect to a receptor protein that is primarily involved in some completely different regulatory function. However, this is irrelevant for the purposes of patentability. The Examiner is overly concerned with determining the exact mode of action of the 4-1BB in vivo. It is not necessary that the applicant know all of the details or even any of the details of the primary role of 4-1BB in vivo. The bottom line is that 4-1BB (by being used to create the monoclonal antibody) has been shown to have a utility in enhancing T cell proliferation. This effect of the treatment described is important to any problem in an organism that results in a low T-cell count (eg. AIDS) or in culturing of cells (secondary utility).

4-1BB can be used to either induce or suppress (by ligand blocking) B-cell proliferation. (See Page 5, lines 10-21) 4-1BB expressing SF-21 cells were used to stimulate resting murine B cells. Mice are extensively used as a model for humans and much research for therapy is performed in mice prior to humans. For example, the "Harvard Mouse" had a great deal of commercial value because of its ability to act a model for testing human compounds. Because of the extensive use of mice for this purpose a great deal of research and tools have been developed for use with mice. Furthermore, there is no requirement that a product have commercial utility, but merely that it is capable of some useful purpose other than solely research. So while the Examiner may not see the commercial utility of stimulating resting murine B cells, it does not mean that such methods do not have patentable utility. Applicant's do not need to demonstrate a human therapy for purposes of 35 U.S.C. §101.

Like any good scientist, the applicant realizes that there is a lot more to learn about 4-1BB, however, this does not mean that there is not a great deal known already. The fact that there is more to know or discover does not mean that which is already known is not true. It is not necessary for the applicant to know all uses of a particular product for there to be patentable utility.

Frankly, there is no invention that could not use further analysis. The entire concept of invention is based upon further discovery and improvement. The specification includes many references to potential new areas of study and further research possibilities but this does not mean that nothing is known about 4-1BB or its function. The effects of 4-1BB have been discovered, specifically, T-cell proliferation and activation and B-cell proliferation and suppression through ligand binding. Doctors know that ibuprofen cures a headache but they know relatively little about how it cures the headache. The applicant has clearly demonstrated how the claimed cDNA can be used to make recombinant 4-1BB which along with the monoclonal antibody raised against this protein and how these products can be used in a utilitarian way.

The specification alleges numerous uses of the claimed cDNA. The Examiner does not present any objective evidence to refute the allegations of utility. The current and parent applications allege a "definite and currently available utility" for the claimed invention. Therefore, the present specifications satisfies the requirement of 35 U.S.C. §101 by teaching the uses for the 4-1BB cDNA, protein and monoclonal antibody. Therefore, the reversal of this rejection is requested.

With Respect to Issue III

The rejected claims 1-3 and 22 under 35 U.S.C. §112, first paragraph, arguing that the specification fails to provide an adequate written description and an enabling disclosure. This rejection is respectfully traversed.

The Examiner states that the applications fails to teach how to use the cDNA recited in claims 1-3 and 22. This is not true.

The cDNA is on deposit and the sequence is provided in the specification. The sequence is described completely both structurally and functionally. The deposit enables those skilled in the art to make and use the sequence. The specification specifically teaches methods of using the claimed cDNA to isolate or make similar sequences, recombinant proteins, fusion proteins, mAb's that enhance T-cell proliferation and activation, and SF-21 4-1BB expressing cells that can be used to induce B-cell proliferation. The specification describes in detail the methods and materials to use the claimed cDNA to accomplish these ends. The Examiner does not present any objective evidence to refute that the described operability or use of the cDNA to make the recombinant protein, baculovirus or sf-21 cells. The utility of such products and methods is discussed above.

Therefore, the present specifications satisfies the requirement of 35 U.S.C. §101 by teaching the uses for the 4-1BB cDNA, protein and monoclonal antibody. The reversal of this rejection is requested.

With Respect to Issue IV

The Examiner rejected claims 1-3 and 22 under 35 U.S.C. §102 arguing that the claims are anticipated by Kwon *et al.* (1989). This rejections is respectfully traversed.

The Examiner stated that the claimed invention is denied the benefit of the filing date of the prior applications as the prior applications do not contain an adequate written

description. After denying the benefit of the earlier filing date, the Examiner rejected claims 1-4 over the applicant's publication which discloses less than the parent application. This denial of priority and rejection are respectfully traversed.

The Examiner states that:

> "The parent application 07/267,577 teaches that 4-1BB is a novel sequence of unknown function. Note p. 2, lines 40-42. In addition, in contrast to the instant application which teaches that 4-1BB is a protein receptor, the parent application suggests that instant cDNA sequence encodes a **lymphokine**, a soluble the protein secreted by a lymphokine."

The Examiner's statements are incorrect. First, the section of text the Examiner refers to merely states that unlike the other transcripts isolated using the novel differential screening technique, isolates 4-1BB and L2G25B were novel sequences that had previously not been characterized. Following, this description is a detailed characterization of the sequences. Secondly, the parent application teaches that "the deduced amino acids of 4-1BB has characteristics of the signal peptide of secretory and membrane-associated protein" (See page 13, lines 7-9). Furthermore, the present specification also teaches that 4-1BB may also have a secreted form (See page 80, lines 17-19 of present application) The line between receptor protein and lymphokine is not as clear as the Examiner suggests. Other proteins are both secreted and expressed on the cell surface. (See page 80, lines 15-22 of present application.)

The current application definitely teaches that 4-1BB is expressed on the cell surface, but the teachings of the parent application ('577) are also enabling. The characterization of 4-1BB as a novel protein involved in the immune system and expressed differentially in T-cells are accurate and one skilled in the art was enabled to make and use the claimed invention at the time of filing of the parent application.

35 U.S.C. §120 read as follows:

"An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application."

Application Serial No. 07/267,577, filed November 7, 1988 disclosed the sequence of the claimed cDNA and refers to a deposit of the cDNA. The specification also taught how to use the cDNA to make a recombinant protein and to isolate the human homologue for 4-1BB. (see page 18, line 37 - page 19, line 28 of '577 application) Both the sequence information and the deposit have long been held to satisfy the enablement requirements of the 35 U.S.C. §112 and the Examiner's position is directly contradictory to long-standing case law.

The '577 application enables those skilled in the art to make and use the claimed cDNA. The Examiner does not state or provide any evidence that the uses described by the applicant are not operable. In fact, the additions in the later applications are proof that the uses taught in the '577 are operable in that the techniques described in the '577 application were used successfully to isolate the human 4-1BB cDNA. Major efforts are to map the Human Genome, and the cDNA described in the '577 application was a useful tool in identifying, mapping and isolating new Human genes.

The denial of the benefit of the earlier filing dates is believed to be improper as the prior applications are enabling and provide an adequate written description of the present invention. If the specification is granted the benefit of priority under 35 U.S.C. §120, the

reference can no longer be applied and the rejection would be improper. Therefore, the applicant's attorney respectfully request that the rejection be reversed.

Conclusion

Applicant believes the claims are patentable over the prior art, and that this case is now in condition for allowance. Based upon the arguments made herein, the applicant requests that the Examiner's rejection of claims 1-3 and 22 be reversed and that claims 1-3 and 22 be allowed.

Respectfully Submitted:
Byoung Se Kwon,

Dated: January 22, 1996

By: _____

Christopher A. Michaels, Reg. No. 34,390
Attorney for Applicant
BARNARD, BROWN & MICHAELS
306 East State Street, Suite 220
Ithaca, NY 14850
(607) 273-1711 (607) 273-2609 (fax)

CERTIFICATE OF MAILING

EXPRESS I hereby certify that this correspondence is being deposited in the U.S. Postal Service as ~~Certified~~ Mail No: EM257817450 with a return receipt requested, in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231 on January 22, 1996

Judy H. Barron

Judy H. Barron

APPENDIX
BOARD OF PATENT APPEALS AND INTERFERENCES
APPEAL BRIEF

In re Application of:	Byoung Se Kwon
Serial No.:	08/012,269
Filed:	2/01/93
For:	NEW RECEPTOR, MONOCLONAL ANTIBODY, LIGAND PROTEIN AND METHODS FOR USE
Examiner:	M. Mosher
Art Unit:	1807
Docket No.:	IND3

The Claims On Appeal

1. A cDNA sequence which encodes for receptor protein 4-1BB.

2. The cDNA sequence of claim 1 having a nucleotide sequence as shown in Figures 2a and 2b.

3. The cDNA sequence of claim 1, identified as p4-1BB deposited at the American Type Culture Collection at 12301 Parklawn Drive, Rockville, Maryland 20852 under ATCC No.: 67852.

22. A DNA selected from the group consisting of:

a) a purified and isolated DNA which encodes the amino acid shown in figures 2a and 2b;

b) nucleotides that can be used as hybridization probes to isolate a sequence of subparagraph a).